10-15-91

PATENTS
Case 26890-CIP

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :

Jacob Berger et al. :

Application No. 07/704,565 : Group Art (not yet known)

Filed May 22, 1991 : Examiner (not yet known)

For TRICYCLIC 5-HT_3 RECEPTOR ANTAGONISTS

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

INFORMATION DISCLOSURE STATEMENT

In compliance with 37 CFR 1.56, 1.97 & 1.98, Applicants direct the attention of the Office to the following documents, listed on the attached Form PTO-1449, which may be material to the examination of this application.

The Lancet, **September 23, 1989**, Page 717 **(Lancet)**

Lancet, discussed on pages 1 and 2 of the application, describes the use of 5-HT_3 antagonists as antipsychotic agents, cognition enhancing agents, anxiolytic agents, and in treating dependency disorders. Lancet also describes the anti-emetic activity of 5-HT_3 antagonists such as ICS 205-930 (tropisetron), ondansetron, and granisetron.

Gastroenterology Clinics of North America, **1989**, *18*, 437 **(Reynolds)**

Reynolds, discussed on page 2 of the application, describes the prokinetic activity of cisapride a 5-HT_3 receptor antagonist.

Trends. Pharmacol. Sci., **1988**, *9*, 141 **(Peatfield)**

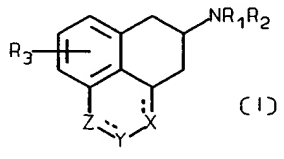
Peatfield, discussed on page 2 of the application, describes the use of the 5-HT_3 antgonist MDL-72222 in treating migraine.

J. Pharmacol. Exp. Ther., **1988**, *245*, 773 **(Scholtysik et al.)**

Scholtysik et al., discussed on pages 2 and 3 of the application, describes the class I and class II antiarrhythmic properties of the 5-HT_3 antagonist ICS 205-930.

PCT Application Publication No. WO 88/04292 **(Szmuszkovicz)**

Szmuszkovicz discloses compounds of Formula I:



(I)

in which:

a dashed line denotes an optional bond;

X is CHR_5, Y is CR_5 or C=O, and Z is NR_4; or

X and Z are CHR_5 and Y is NR_4; or

Y and Z are CHR_5 and X is NR_4;

R_1 and R_2 are hydrogen, C_{1-3} alkyl or C_{1-4} alkyl, with the proviso that when R_2 is C_{1-4} alkyl R_1 is hydrogen; or

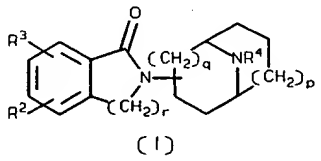
NR_1R_2 is azetidinyl, pyrrolidinyl, piperidinyl or morpholinyl;

R_3 is hydrogen, fluoro, chloro, bromo, C_{1-3} alkyl, C_{1-3} alkoxy, trifluoromethyl, C_{1-3} alkylcarbonyloxy, phenylcarbonyloxy or benzylcarbonyloxy; and

R_4 is part of a double bond when the optional bond is present or is hydrogen C_{1-3} alkyl or $C(O)R_6$ wherein R_6 is C_{1-3} alkyl or benzyl; and the acid addition salts and use (i.e., in treating psychotic behavior) thereof.

European Patent Application Publication No. 0 093 488 **(Hadley)**

Hadley discloses dopamine receptor antagonists of Formula I:



(I)

in which:

r is 1 or 2;

p and q are independently 0 to 2;

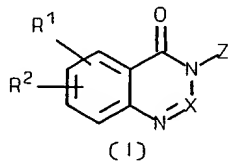
R_2 and R_3 can be independently selected from, *inter alia*, hydrogen, halogen, C_{1-6} alkyl, amino and aminocarbonyl; and

R_4 can be, *inter alia*, C_{1-7} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-2} alkyl, or a group $(CH_2)_tR_7$

where t is 1 or 2 and R_7 is thienyl, or is phenyl optionally substituted by one or two substituents selected from C_{1-4} alkoxy, trifluoromethyl, halogen, carboxy, esterified carboxy, or C_{1-4} alkyl further optionally substituted by hydroxy, C_{1-4} alkoxy, *in vivo*, hydrolysable acyloxy, carboxy, or esterified carboxy; and the enantiomers, racemates, compositions, pharmaceutically acceptable salts, solvates, *N*-oxide derivatives, processes for preparation, and uses (i.e., in treating emesis, impaired gastro-intestinal motility, and CNS disorders) thereof.

U.S. Patent No. 4,959,367 **(King)**

King discloses 5-HT receptor antagonists of Formula I:



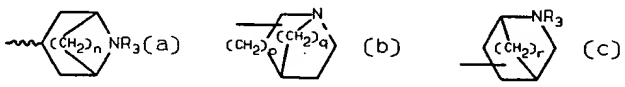
(I)

in which:

X is CH or N, preferably N;

R_1 and R_2 can be independently selected from, *inter alia*, hydrogen, halogen, C_{1-6} alkyl, amino, amino carbonyl, (C_{1-7} acyl)amino, (C_{1-6} alkyl)amino, and di(C_{1-6} alkyl)amino; and

Z is a group selected from Formula (a), (b) or (c):



in which:

n is 2 or 3;

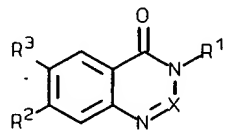
p is 1 or 2;

q and r are 1 to 3; and

R_3 and R_4 are C_{1-4} alkyl; and the enantiomers, racemates, compositions, pharmaceutically acceptable salts, solvates, *N*-oxide derivatives, processes for preparation, and uses (i.e., in treating migraine, cluster headaches, trigeminal neuralgia, visceral pain, arrhythmia, obesity, emesis, CNS disorders, and gastrointestinal disorders) thereof.

J. Med. Chem., **1990**, *33*, 2942-2944 **(Salituro et al.)**

Salituro et al discloses compounds of the generic formula:



in which:

X is CH or N;

R_2 is hydrogen, amino or nitro;

R_3 is hydrogen or chloro, and

R_1 is *endo*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl or (±)-1-azabicyclo[2.2.2]oct-3-yl; and the processes for preparation thereof; and reports substantial loss in 5-HT_3 receptor antagonist activity when X is CH.

The following references were cited by the Examiner during prosecution of the parent application (Application No. 07/442,082), filed November 28, 1989:

U.S. Patent No. 4,309,543 **(Keeley)**

U.S. Patent No. 3,896,132 **(Bernauer et al.)**

U.S. Patent No. 3,341,528 **(Shavel et al.)**

Keeley, Bernauer et al., and Shavel et al. were cited as examples of other and material different processes by which the compounds of the invention could be made in support of a restriction requirement between claims to compounds and claims to the process of making the compounds.

U.S. Patent No. 4,571,396 **(Hutt et al.)**

Hutt et al. was listed by the Examiner on the Notice of References cited but not referred to in the text of the Examiner's explanation.

Chemical Abstracts, **1978**, *89*:100352x **(Komatsu et al.)**

Chemical Abstracts, **1988**, *108*:221716p **(Hilbert et al.)**

Komatsu et al. and Hilbert et al. were cited as examples of methods for treating gastro-intestinal disorders and CNS disorders, respectively, in support of a rejection of a generic claim to methods of use as an improper Markush grouping.

Copies of the above documents are provided herewith. The Examiner is requested to consider these documents, and to indicate that this has been done by signing and returning a copy of the Form PTO-1449.

Respectfully submitted,

Wayne W. Montgomery

Wayne W. Montgomery
Attorney for Applicants
Reg. No. P-35,016

3401 Hillview Avenue
P.O. Box 10850
Palo Alto, California 94303

(415)855-5564
September 10, 1991
676.WP

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on Sep. 10, 1991
(Date of Deposit)

Wayne W. Montgomery P-35,016
Name of applicant, assignee or Registered Rep.

Wayne W. Montgomery 9/10/91
Signature Date